CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020772

MEDICAL REVIEW(S)

Pages: 26 through 50

TABLE 5
NDA 20-772

Summary of the Study Population, Main Features of the Trial, Groups Being Compared and Remarks on the Adequacy of the Control Clinical Trials Presented by the Sponsor in Support of the Efficacy of SUCRAID™ in the Treatment of CSID

Study No./ Protocol No. Publication	Study Population	Main Features of the Trial/ Groups Being Compared	REMARKS
S-1 (OMC-SUC-1) W.R. Treem et al. Gastroenterology 105:1061-1068 (1993) [n=13]	M and F patients, 8 mo. to 28y of age in whom the diagnosis of CSID was confirmed by determination of disaccharide enzyme activity (DEA) in biopsy samples collected during UGI endoscopy from the duodenum. Verification of the correct diagnosis was based on results of the BHT with both sucrose [pts (+) with respect to sucrase deficiency] and lactose challenges [pts (-) with respect to lactase deficiency].	Multicenter, randomized, controlled trial, comprised of two phases. **Phase 1** • BHT: sucrase vs placebo [one week, two single doses given one week apart]. **Phase 2** • Pts. on a normal sucrose diet • Dose Response, sucrase in 4-doses (dilutions) in random order (4 Tx groups): 1:100 vs 1:1,000 vs 1:10,000 vs 1:100,000 for 14 days each, given as 1 ml per meal or snack added to 1 ounce of liquid (water, milk, juice, infant formula)	• Adequate design. • Primary Efficacy Variables included total stools and the total symptom score, collected during the dose-response phase. • Secondary Efficacy Variables included peak, peak minus baseline, and total breath H_2 output (AUBHC), as well as individual and total symptom scores (from the BH phase); and total watery, soft, formed and hard stools, average daily stools, average and total individual symptom scores, average total symptom scores, and comparison of asymptomatics, defined post-hoc (from the dose-response phase).
S-2 (OMC-SUC-2) W.R. Treem et al. Ms. in preparation [n=28]	M and F patients, 5 mo. to 10y of age. Ibid	Multicenter, randomized, controlled trial, comprised of two phases: **Phase 1** • BHT, consisting of 1. placebo, 2. yeast sucrase and 3. yeast sucrase plus milk. **Phase 2** • Pts. on a normal sucrose diet • Dose Response, sucrase in 4 doses (dilutions) in random order: full strength enzyme vs 1:10 vs 1:100 vs 1:1,000 administered ca. 5 min. after beginning each meal, added to 2 to 4 ounces of water for 10 days each, given as 1 ml per meal or snack if Bwt <15 Kg, 2 ml or snack if Bwt ≥15 Kg.	• Adequate design. • Primary Efficacy Variables as in OMC-SUC-1 • Secondary Efficacy Variables as in OMC-SUC-1 In both studies, efficacy is demonstrated by analyses of results on the primary efficacy variables from the dose-response phase (4 strengths of enzyme). Efficacy is supported by results of analyses from the breath test (phase 1) and gastro-intestinal symptoms from both phases.

Reviewer's Original Table

VII. STUDY S-1 (OMC-SUC-1)[25]

"Evaluation of Sucrase Enzyme Replacement in Patients with Sucrase-Isomaltase Deficiency"

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1. Objectives

In the protocol, the following three objectives were listed:

(1) To further characterize the activity, pH, and temperature stability, purity, and proper storage of the liquid sucrase preparation [YS].

(2) To test the efficacy of the liquid sucrase preparation in abolishing or ameliorating diarrhea, flatulence, abdominal pain, and breath hydrogen (H_2) excretion in patients with congenital sucrase-isomaltase deficiency given in oral sucrose challenge.

(3) To establish a dose range of the yeast-derived liquid sucrase preparation which allows the consumption of a normal sucrose-containing diet.

Of the three above-listed objectives, no mention was made about objective (1) in the Clinical Report.

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[25] Date of Final Report: 28 March 1997.

2. Study Population (Table 6)

In this Table, the characteristics of the study population are summarized. Included were patients of any age who provided informed consent (or if patient was younger than 18y old, the IC was provided by a parent/legal guardian) in whom the diagnosis of **CSID** was confirmed..

TABLE 6
Study S-1 (OMC-SUC-1)

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• Patients were recruited from the clinical practices of the members of the North American Society for Pediatric Gastroenterology and Nutrition • Appropriate clinical history. • Small intestinal biopsy with measurement of disaccharidase levels showing sucrase activity of <10% of controls with normal lactase levels and normal or decreased maltase activity. • Normal villous architecture or only mild villous atrophy of the small bowel. • A positive BHT showing a rise in BH of greater than 20 parts per million (ppm) over baseline after an oral sucrose challenge of 1.0 - 2.0 g/Kg, with a negative lactose BHT.	No exclusion criteria were specified in the Protocol.

Reviewer's Original Table

3. Randomization/Treatment Regimen/Compliance

- The sponsor notes that, with respect to the BH phase, the treatment sequences in the database were based on documentation provided by the PI and did not necessarily agree with the order of the dates of the BHTs recorded on the CRFs.[26]

- With respect to the dose-response phase, the treatment sequence actually used was different for some patients than the randomized sequence pre-determined before the start of the trial. For six of the patients enrolled (Patient Nos. 3, 4, 6, 7, 11, 12), the actual treatment sequence used could not be verified independently in the study source documents.[27]

[26] The BHT Order Key indicated the actual sequence utilized and was presented in sponsor's Appendix 17.3.

[27] Sponsor's Appendix 17.3 listed the actual and randomized (if known) treatment sequences for each patient.

- Following 3 days of a sucrose-restricted diet and a 12-h fasting interval, each patient underwent two BHTs, separated by one week. The nature of the tests was as follows:

    1) The patient was orally administered 2 g/Kg Bwt of sucrose up to a maximum of 60 g as a 20% solution in water, followed immediately by 1.0 mL of full strength YS mixed with 29 mL of sterile water;

    2) The patient was orally administered 2 g/Kg Bwt of sucrose followed immediately by 30 mL water and no YS (placebo).

- At the conclusion of the BHTs, each patient was entered into an eight-week (14 days x 4) dose-response phase, and instructed to comply with a diet containing normal amounts of sucrose and starch for four consecutive 14-day periods.

    - During this time, each patient administered four different YS preparations (one preparation per 14-day period) in bottles marked as A, B, C and D.

    - Each vial contained one of the following concentrations of YS: 1:100 dilution, 1:1000 dilution, 1:10,000 dilution or 1:100,000 dilution.

    - The patients were instructed to administer 1.0 mL of the enzyme solution further diluted in 2 to 4 ounces on water, juice, milk or infant formula and consumed with each meal or snack.

- The sponsor notes that specific measures of compliance were not stipulated in the protocol. However, the study coordinator was in frequent (at least weekly) telephone contact with the patient or patient's parent to discuss study compliance.

4. Trial Design/Blinding

Study S-1 was a double-blind, randomized, controlled, two-phase trial.

- Phase 1

  This was a BH evaluation where patients were asked to abstain from eating sucrose for at least 3 days and to fast totally for 12h prior to each BHT. During this phase, patients received each of two single-dose treatments in random order: YS and placebo (water without YS). These 2 treatments - which were separated by a period of one week - were given immediately after ingesting 2 g/Kg Bwt of sucrose (challenge).

- Phase 2

  Following the completion of the BH phase (phase 1), patients entered into an eight-week, randomized, crossover, double-blind, dose-response phase. Patients received four consecutive 14-day treatments assigned in random order: A=1:100 dilution of the full strength sucrase, B=1:1000 dilution, C=1:10,000 dilution and D=1:100,000 dilution. Each patient was administered each of the four treatments for a period of 14 days, while on a normal sucrose diet. There was no wash-out period between treatments.

Blinding

- The study qualifies as double-blind (although not in the customary sense) because both the patient and the patient's parent/guardian were blinded to the treatments given during phase 1 and 2 of the trial.

  - The investigator, however, was unblinded with respect to the treatment sequences. During the dose-response phase, the four different yeast sucrase dilutions (doses) were in bottles labeled only as A, B, C and D, and recorded on the CRF (patient daily diary) by the patient or parent as he/she administered each treatment.

  - It is worth noting, however, that the two primary efficacy parameters and all secondary efficacy measures [except the BH values] were recorded on stooling and symptom diaries completed by the patients or the patients' parent or guardian. All these participants were blinded with respect to the treatment conditions.

5. Test Medications/Concomitant Medications

The sponsor notes that liquid yeast sucrase is used commercially to hydrolyze unrefined sucrose solutions (e.g., sugarcane juice to produce molasses). It has also been used in the preparation of cordial and cream center candies. The **liquid yeast sucrase product** used in Study S-1 contained 9000 IU/mL (± 10%) of sucrase enzyme activity and has been in continuous production by Universal Foods Corporation (Milwaukee, WI) for more than a decade. This product has been approved as a food grade material by the FDA, under FDA provision CFR 170.30, a regulation that grants GRAS status through experience to food products commonly used as food before January 1, 1958.

Concomitant medications taken during the trial were recorded on the CRF. The sponsor notes, however, that if a concomitant medication was collected during the period between the end of the BH phase and the beginning of the dose-response phase, and that time period was greater than 2 to 4 weeks, the concomitant medication was not included in the database.

6. Study Execution

- Demographic information, disease history and symptom history were collected from patients that met the inclusion criteria and signed an IC.

- Patients were then asked to abstain from all dietary sucrose for at least 3 days before each BHT and to fast totally for 12h immediately prior to each BT.

- The two BHTs were randomized, blinded and separated by a period of at least one week.

  - Breath samples were obtained and analyzed for hydrogen content using GC.

  - All BHTs were carried out for a period of 3h, immediately following ingestion of a standardized sucrose load, and BH levels obtained every 30 min.

  - During the tests, and for 8h following each BHT, patients recorded symptoms of diarrhea, abdominal pain, gas, N&V.

- It is to be noted that the actual manner in which the trial was conducted differed somewhat from what was described in the protocol.

  - Firstly, BHTs for some patients may have occurred more than one week apart due to one or more of the following:

    (1) the occurrence of an elevated BH baseline value. This could have been due to an inadequate pre-test fast or sucrose dietary restriction, resulting in the test having to be repeated later;

    (2) the occurrence of an AE due to an intercurrent illness;

    (3) the use of previous CSID diagnostic test results in place of the placebo test.

  - Secondly, the occurrence of diarrhea, gas, bloating and cramps were also recorded during each three hour BHT period, as well as for the 8h following the BHT as called for in the protocol.

  - Lastly, only symptom severity (0=None, 1=Mild, 2=Moderate and 3=Severe),[28] and not symptom frequency were recorded during this phase.

[28] For the purpose of Study S-1, "Mild" was defined as lasting less than 5 minutes and not interrupting normal activity; "Moderate" was defined as lasting 5-30 minutes and interrupting activity but resolving rapidly; and "Severe" was defined as lasting more than 30 minutes and causing a cessation of normal activity for a prolonged period of time.

7. Efficacy Evaluations and Criteria for Efficacy

Primary Efficacy Assessments

These included total stools and the total symptoms score collected during the dose-response phase.

Secondary Efficacy Assessments

All other measurements assessed during the dose-response phase and the BH phase were secondary.

For the BH phase, these included peak, peak minus baseline, and total BH output (area under the BH versus time curve, AUC), as well as individual and total symptom scores.

For the dose-response phase, these included total watery, soft, formed and hard stools, average daily stools, average and total individual symptom scores, average total symptoms scores, and comparison of the proportion of asymptomatics [which was defined post-hoc].

a. Breath Hydrogen Phase

During this phase, peak, peak minus baseline, and total BH output (AUC) were calculated based on BH results obtained at baseline and for a period of 3h, at intervals of 30 min.

In addition, each patient reported severity of symptoms (diarrhea, gas, bloating and cramps) during the BHTs and for a period of 8h following each test. For each patient, the most severe response during, or after, the BHT was assessed for each symptom.

Finally, a total symptoms score was obtained for each patient by summing the most severe response recorded during or after the test across the four symptoms.

b. Dose-Response Phase

During this phase, the number of stools and severity of g.i. symptoms (gas, bloating, nausea, vomiting and abdominal cramps) were reported by each patient on a **daily basis** during each treatment period of this phase.

As already mentioned, the symptoms were assigned values of 0=none, 1=mild, 2=moderate or 3=severe. For all patients, period totals for each efficacy measurement (number of stools and g.i. symptoms) were calculated for each treatment by summing over the 14-day period. A total symptoms score was obtained for each patient by summing the total responses of all five symptoms across each period. Daily averages were calculated for each symptom individually, and for the total symptoms score, by dividing the period total for a patient by the number of days the patient had nonmissing data.

In addition to the above protocol-stipulated assessments, after the dose-response phase data were summarized, a post-hoc efficacy measurement [asymptomatic (YES/NO)] was defined as follows: First, on each day of each 14-day period, each patient was assigned a value of 1=yes if there were no watery stools and ratings of none or mild for all g.i. symptoms on that day; a value of 0=no if there was at least one watery stool or a rating of moderate or severe for at least one g.i. symptom on that day; or, a value of missing if it was unable to be determined from the data whether or not the patient was asymptomatic. Next, the percent of days with asymptomatic response was calculated by summing over the 14-day period for each treatment, then dividing by the total number of days with nonmissing responses, and multiplying by 100. If the percent of days with **asymptomatic response** was at least 70%, the patient was considered to be **asymptomatic** for that period.

8. Safety Assessments

The handling of AEs and laboratory evaluations was adequate.[29]

Removal of Patients From Trial

Patients could withdraw from the trial at any time.

9. Data Handling Procedures/Validation of Data

In the clinical report, pages 24 through 26, the sponsor notes that a clinical research monitor (CRM), contracted by Orphan Medical, was responsible for ensuring the validity of the data recorded on the CRFs.

> "All efficacy data collected on the original CRFs were transcribed onto blank CRFs by the CRM. With respect to stool consistency measures, if on the original CRF a given day was left blank, NI (Not Indicated) was transcribed onto the blank CRF, to be interpreted as missing data. The CRM was responsible for verifying the accuracy of all transcriptions. AEs and concomitant medications listed on the CRFs were extracted by the CRM and entered into WordPerfect® documents. Demographic characteristics, disease history, and symptoms present were provided to in the form of an Excel® spreadsheet.
>
> "All data management and data entry were . All data from the transcribed CRFs were entered using a single-entry method. Data entry of the trial was accomplished using the Paradox® software package. Upon entry completion, these data were transferred into SAS® datasets for analysis. Data from the Excel® spreadsheets were converted to SAS® and subsequently entered into the database. Data from the WordPerfect® files were converted to Microsoft® Word, but were not entered into the database.

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[29] As noted by the sponsor, safety assessments consisted of adverse events (AEs) reported at any time during the trial. This included events that were reported by the patient on the CRFs, as well as any significant AEs which occurred in the doctor's office during BH testing. However, any AE that was collected during the period between the end of the BH phase and the beginning of the dose-response phase was not included in the database if that time period was greater than two to four weeks. AEs were recorded regardless of relationship to trial drug. All AEs were compiled by the clinical research monitor and provided AE reporting included the Investigator's determination of relationship to trial drug (1=concurrent illness, not related; 2=possibly related; 3=probably related; 4=definitely related; or 5=unknown if related), phase of the trial the patient was in during the AE, and any resolution recorded on the patient's CRF.

"Edit checks and consistency checks were incorporated into the data management process. Data identified as erroneous from these checks or any other source, or key data which were missing, were explained on data clarification forms (DCFs) and referred to the CRM, or if necessary, to the Investigator, for resolution. With respect to g.i. symptoms, if on the transcribed CRF a given day was left blank for any symptom, a zero was entered into the database to indicate that there was no occurrence of that symptom on that day. Upon return of the DCFs, the data were updated wherever necessary. All updates were checked for accuracy and consistency.

"A full audit was performed on the complete database. This entailed a 100% check of all data, and included an overall comparison of data to the CRFs and returned DCFs."

10. Statistical Methodology

a. Generalities

Data analyses were performed by For patient accountability, protocol deviations and demographic characteristics, tabular summaries were presented overall. For all efficacy tables, tabular summaries were presented by treatment. Continuous outcome variables were summarized by presenting the sample size, mean, standard error of the mean, median, minimum and maximum values. Categorical outcome variables were summarized by presenting the number and percentage of patients in each category. Percentages were rounded to the nearest whole number and were calculated using the total number of patients (presented on the first line of the table) as the denominator, unless otherwise noted. In some cases, individual patient listings of results served as primary tables. All data collected for this trial were provided in the data listings (as SAS Proc Prints) in sponsor's Appendix 17.4.

All tests to assess treatment efficacy were considered statistically significant if the p-value was ≤ 0.050. P-values were rounded to three decimal places. P-values less than 0.001 were reported as 0.001 in all tables. No adjustments for multiplicity were made; however, a step-down procedure was used to interpret statistical significance (sponsor's Section 9.7.2, Dose-Response Phase).

Computations for the statistical methodology described in this report were performed using SAS®.

b. Determination of Sample Size

Study S-1 was set to collect preliminary data relative to YS-treated CSID patients. As such, no predetermined sample size was defined in the protocol. Nonetheless, a sample size of 20 patients was anticipated.

c. Patient Populations Analyzed

Two patient populations were analyzed: the efficacy population and the safety population.

Efficacy Population

This was comprised of those patients who received at least one dose of any of the yeast sucrase (YS) concentrations [1:100 dilution, 1:1000 dilution, 1:10,000 dilution or 1:100,000 dilution] during the dose-response phase.

Safety Population

This was comprised of all patients who received at least one treatment [placebo or YS] during the breath hydrogen phase.

All results were presented for the efficacy population with the exception of withdrawals, AEs and concomitant medications, which were presented for the safety population.

d. Patient Enrollment and Accountability

The number of patients that were screened, randomized to the dose-response phase, and who withdrew prior to randomization were presented in tables, in addition to the number of patients for whom the randomization treatment sequence cannot be verified.

For the BH phase, the number of patients who received at least one treatment (i.e., the safety population) were tabulated. Of the patients in the safety population, frequencies and percentages were presented for those patients who completed the BH phase. A listing of patients who withdrew after receiving treatment was provided. This list included the reason for withdrawal and the phase and period in which the withdrawal occurred. For the dose-response phase, frequencies and percentages were presented for those patients who received at least one treatment [i.e., the efficacy population], who completed, and who withdrew. Also presented were the number and percentage of patients who withdrew from the trial after any treatment. Finally, the number and percentage of patients with protocol deviations were tabulated. A listing of patients with protocol deviations was provided.

e. Demographic and Background Characteristics

Descriptive summaries of demographic data, including age, gender, and weight were presented. Age was calculated using date of birth and date of IC. A listing of disease history for all patients was also provided. This included the pathology report, method of diagnosis, and result of each disaccharidase measure.

f. Concomitant Medications

A listing of all patients who received concomitant medications during the trial was provided.

g. Analyses of Efficacy

i) Breath Hydrogen Phase

- For continuous variables, BH output was summarized with descriptive statistics for each treatment (placebo or YS), at baseline (0 min), and every 30 min. up to 3h. Peak BH, peak minus baseline, and total breath hydrogen output (AUC) were also summarized.
- For peak minus baseline and total BH output, negative values were converted to zero before descriptive statistics were calculated. Total BH output was calculated as the area under the curve (AUC) of breath hydrogen output over time using the trapezoidal rule.[30]
- Treatments were compared for peak, peak minus baseline, and AUC using an analysis of variance (ANOVA) model with effects for treatment and patient. Ninety-five percent confidence intervals and p-values for pairwise treatment comparisons were obtained based on the ANOVA least squares means.
- During each treatment period of the breath hydrogen phase, and for the following 8h, severity of g.i. symptoms (diarrhea, gas, bloating, and cramps) was recorded as none, mild, moderate and severe.
- For each symptom, the most severe response recorded during or after the test was summarized for each treatment with frequencies and percentages.
- A total symptoms score, obtained by summing the most severe response across the four symptoms for each patient, was also summarized with frequencies and percentages.
- P-values for pairwise treatment comparisons of each symptom and the total symptoms score were obtained from a Wilcoxon signed-rank test of the difference in response between the two treatments.

ii) Dose-Response Phase

- For each patient, period totals for each efficacy measurement (number of stools, stool consistency measures, g.i. symptoms) were calculated for each treatment by summing over the 14-day period.
- A total symptoms score was obtained for each patient by summing the total responses of all five symptoms across each period.
- Daily averages were calculated for number of stools, individual symptoms, and the total symptoms score by dividing the period total for a patient by the number of days the patient had nonmissing data.
- Total stools, average daily stools, and total stool consistency were summarized for each treatment with descriptive statistics for continuous variables.
- Totals and averages of individual symptoms, the total symptoms score, and the daily average of the total symptoms score were each categorized, and then summarized with frequencies and percentages. The cut points of the categories were defined such that each category contained at least 10% of responses across the treatments.
- Statistical treatment comparisons were performed for total stools, averages of individual symptoms, and the total symptoms score.
- P-values for pairwise treatment comparisons were obtained from a Wilcoxon signed-rank test of the difference in response between the two treatments.
- The two higher concentrations (1:100 and 1:1000 dilutions) were also compared to the two lower concentrations (1:10,000 and 1:100,000 dilutions) with a Wilcoxon signed-rank test.

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[30] For this calculation, missing values that occurred before the last time point were interpolated, and missing values that occurred at the last time point were assigned the value of the previous time point.

- **Multiple comparisons** were addressed by a step-down procedure. The primary comparisons were for the two higher versus the two lower dose levels for total stools and the total symptoms score. Within each of these measurements, if the primary comparison was significant (p-value ≤0.050), the six pairwise treatment comparisons were also evaluated for significance. Given that the primary comparison was significant for the total symptoms score, this comparison was also evaluated for each individual symptom, and, when significant, pairwise treatment comparisons for the individual symptom were also evaluated.

- The number and percentage of patients who were asymptomatic were summarized by treatment group. Additionally, p-values for pairwise treatment comparisons were obtained from McNemar's test, a nonparametric procedure.

11. Results

[NOTE: For simplification of presentation purposes, only Tables originating from the Medical Reviewer and/or key Tables and/or Figures presented by the sponsor, are reproduced in this review.]

A. Patient Accountability/Protocol Deviations
[Sponsor's Tables 1.0, 2.0, 4.0 and 4.1]

- A total of 16 patients were screened for this trial. Of these, 14 entered and completed the BH phase of the trial (safety population).

- 13 entered the dose-response phase of the trial (efficacy population). Of these,

  - 11 completed the dose-response phase, having received all 4 of the assigned treatments

  - 2 withdrew from the dose-response phase of the trial.

- A total of 4 patients [#3, #4, #11 and #12] withdrew from the trial at some point after treatment and were eventually lost to follow-up.

- 12/13 patients in the efficacy population had **at least one deviation** from the study protocol.

  - For 4 of these patients, the treatment sequence used in the dose-response phase could not be verified from the study documents.

  - 7 had incomplete diary information

  - 4 were non-compliant with respect to sucrose loading dose used in the BHTs.

  - 1 each was non-compliant with respect to the dose-response treatment sequence, the performance of the BHTs and time intervals in the follow-up visit schedule.

B. Demographics/Disease History/Concomitant Medications
[sponsor's Tables 5.0, 3.0, 6.0 and Appendix 17.4.1]

- Of the 13 patients in the efficacy population, 10 were females, 3 males.
- The mean age was 8.2 years
- The mean weight was 24.3 Kg
- The results of the disaccharide enzyme assay (DEA) were not available for 2 patients (#3 and #8). For these 2, the diagnosis of CSID was confirmed by BH testing and carbohydrate tolerance testing, respectively.
- The accompanying pathology report was not available for 3 patients [#3, #8 and #15].
- Pathology reports for two patients [#6 and #7] revealed abnormal villous architecture. However, in both patients, the disaccharidase levels in the duodenal mucosa were non-existing: palatinase = 0; sucrase = 0.
- A tally of the disaccharidase levels in all 16 patients screened is given in Table 7.

TABLE 7
Study S-1 (OMC-SUC-1)

Results of Pathology Evaluations on Disaccharidases
(All Patients Screened)[a]

ENZYME	DISACCHARIDASE LEVEL		
	0	Some	Normal
Sucrase	8	1 (15.2) 1 (14.7) 1 (15.4)	
Paltinase (Isomaltase)	7	1 (8.0) 1 (2.5) 1 (1.5)	
Lactase	NONE		11 (10.6 to 101.5)
Maltase	NONE		11 (26.8 to 86.8)

Reviewer's original table

a) The accompanying pathology report was not available for 3 patients (#3, #8 and #15). In spite of this, the diagnosis of CSID in patient #15 was based on results of the DEA. In patient #3 the diagnosis was based on results of the BHT only. In patient #8, the diagnosis was based on results of the CTT (carbohydrate tolerance test).

In 4 patients (#1, #2, #4 and #9) the diagnosis included results of both the DEA and the BHT.

- 5 patients took concomitant medications during the trial. These[31] medications are not expected to confound efficacy or safety results.

C. Efficacy

1) Primary Efficacy Parameters (Table 8)

- Refer to upper panel of Table 8.

There were no statistically significant differences between any of the groups, when compared in a pairwise fashion in either total stools (summed up over a 14-day period) or mean stool per day (averaged over the 14-day period).

- Refer to the lower panel of Table 8.

For total symptoms (representing the sum of total gas, total bloating, total nausea, total vomiting, and total cramp scores over the 14-day period) there were statistically significant differences only between the lowest (1:100) vs highest (1:100,000) dilution of enzyme tested. Note, however, that the number of patients per subgroup (total symptoms) was very small. All other pairwise comparisons yielded differences that were non-significant in clinical and statistical analyses.

2) Secondary Efficacy Parameters

a) Breath Hydrogen Phase

- The BHT results are summarized in Table 9.[32] Depicted are the mean and the median at 6 time-points starting at 30 min. from baseline (time 0) to 180 min. Whether one compares the mean or the median, the BH output was always higher with placebo than with enzyme treatment.

- The BH excretion results are better appreciated in Fig. 6. The median changes (upper graph) indicate that in the placebo-treated CSID patients, significant BH excretion-indicative of sucrose malabsorption-starts ca. one hour after the sucrose solution is ingested, reaches a peak at 90 to 120 min, after which it begins to decline. These kinetics of BH excretion are to be contrasted to those seen when the sucrase enzyme is taken with the sucrose load. In the sucrose-treated patients, only a slight change in BH excretion (median) occurred.

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[31] These concomitant medications included: Triaminic®, Amoxil®, Amphojel®, Mylanta®, Levsin®, Imodium®, Panadol®, and unspecified muscle relaxants.

[32] Data were available for 12 of the 13 patients in the efficacy population. A listing of individual patient BH data was found in sponsor's Appendix 17.4.3. BH data were not collected on Patient 4. Data collected on patients 11 and 12 were not analyzed because these were not included in the efficacy population. A listing of the (erratic) BH data for these 2 patients was presented in sponsor's Table 7.2.

TABLE 8
Study S-1 (OMC-SUC-1)

Results of Primary Efficacy Parameters

	TREATMENT/DILUTION			
	1:100 [A]	1:1000 [B]	1:10,000 [C]	1:100,000 [D]
I. Total Stools[a]///Average Stool per Day[b]				
	[n=13]	[n=11]	[n=13]	[n=11]
Mean (median)	24.5 (24)	20 (20)	24.4 (22)	22.7 (23)
Mean (median)	1.8 (1.7)	1.4 (1.4)	1.8 (1.6)	1.7 (1.7)
Statistics (p-value)[c]	A vs B N.S. / A vs C N.S. / A vs D N.S. / B vs C N.S. / B vs D N.S. / C vs D N.S.			A+B vs C+D N.S.
II. Total Symptoms				
	[n=13]	[n=11]	[n=13]	[n=11]
0	1 (8%)	2 (18%)	1 (8%)	2 (18%)
1-7	1 (8%)	4 (36%)	1 (8%)	3 (27%)
8-12	3 (23%)	0	4 (31%)	2 (18%)
13-20	4 (31%)	2 (18%)	3 (23%)	1 (9%)
21-35	1 (8%)	2 (18%)	2 (15%)	3 (27%)
>35	3 (23%)	1 (9%)	2 (15%)	0
Statistics (p-value)[d]	A vs B N.S. / A vs C N.S. / A vs D **0.020** / B vs C N.S. / B vs D N.S. / C vs D N.S.			A+B vs C+D N.S.

Reviewer's original table

a) Based on total number of stools (summed up) over a 14-day period
b) Averaged over a 14-day period
c,d) p-values obtained from a nonparametric Wilcoxon signed-rank test on pairwise treatment comparisons.

TABLE 9
Study S-1 (OMC-SUC-1)

Results of Secondary Efficacy Parameters
Breath Hydrogen Phase: Breath Hydrogen Output

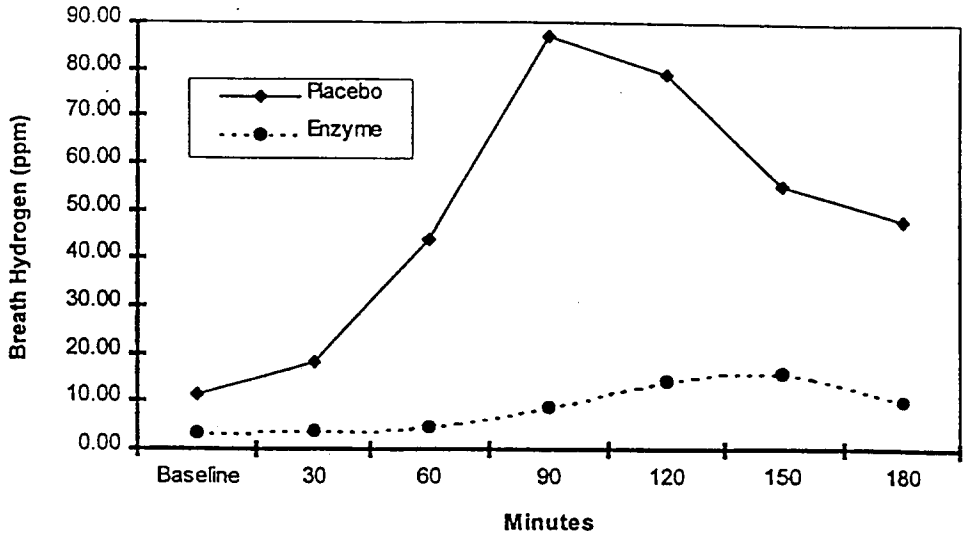
			Time Point from Baseline (min)					
Treatment Group	Evaluation Parameter	Baseline [n=13]	30 [n=13]	60 [n=13]	90 [n=13]	120 [n=13]	150 [n=13]	180 [n=13]
Breath Hydrogen Output (ppm)								
Placebo	n Mean Median	12 21.0 11.5	12 32.1 18.0	12 62.3 44.0	11 90.0 87.0	12 109.4 79.0	12 101.8 55.5	11 110.6 48.0
Enzyme	n Mean Median	12 5.1 3.5	12 6.1 4.0	12 22.1 4.5	11 47.1 9.0	12 62.2 14.4	11 75.3 16.0	11 74.2 10.0

	Evaluation Parameter	Peak [n=13]	Peak-Baseline [n=13]	AUC[a] [n=13]	
Breath Hydrogen Output (ppn)					
Placebo	n Mean Median 95% C.I.	12 129.7 105.5 [116.0, 143.3]	12 108.7 81.6 [92.2, 125.1]	12 13647.4 9540.0 [11859.1, 15435.6]	
Enzyme	n Mean Median 95% C.I.	12 82.8 29.5 [69.2, 96.5]	12 77.8 26.0 [61.3, 94.2]	12 7209.0 2137.5 [5421.0, 8997.0]	
Statistics (p-values)	(ANOVA)	**0.001**	**0.014**	**0.001**	

Reviewer's Table, based on sponsor's Table 7.0 (pages 117-119)with major modifications. The S.E., Min. and Max. values have been omitted and fractions of ppm have been rounded off to one decimal, for clarity of presentation.

a) AUC = Area under the curve. Missing values that occurred before the last time point were interpolated. Missing values that occurred at the last time point were assigned the value of the previous time point.

NOTE: Negative values for peak minus baseline and AUC were converted to zero.
p-values and 95% confidence intervals (C.I.) about least squares means were obtained from ANOVA models with effects for treatment and patient.
p-values for the pairwise treatment comparison placebo vs enzyme are not presented in the table, as the results are the same as for the treatment effect p-values.
One patient had missing data at all time points; three patients had missing data at various time points.



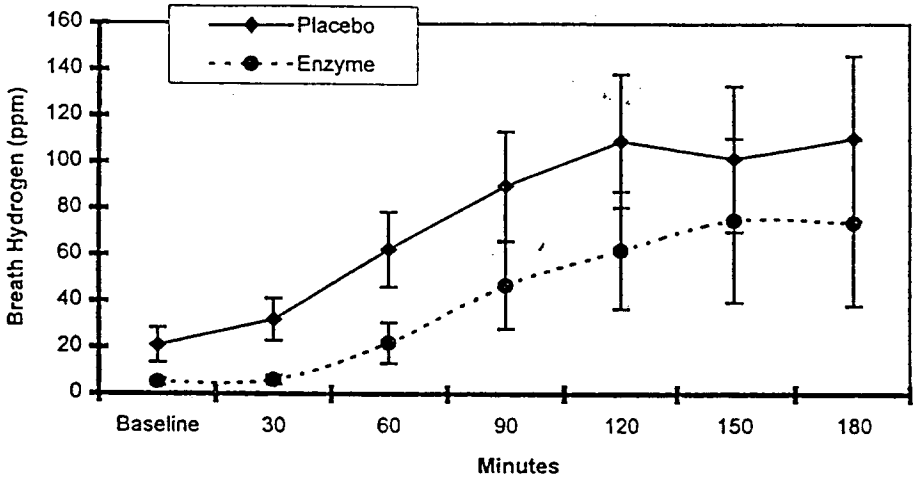


Fig. 6 - *Study S-1 (OMC-SUC-1): Breath Hydrogen Excretion Following Pre-treatment with the oral Sucrose Loading dose of 2 g/Kg and Oral Treatment with Either the Sucrase or placebo (water) test dose.*

Upper Graph: median values
Lower Graph: Mean ± S.E.M.

- In the lower graph in Fig. 6 the BH data are plotted as mean and S.E.M. The pattern in this graph is not very dissimilar to that seen when plotting median data. But the mean data give a) an indication of the relatively high intersubject variability in BH excretion and b) the greater effect of individual outlier responses on the mean vs the median values shown in the upper graph.

- The reader is referred to the lower panel of Table 9, where comparisons are made between the two treatments (sucrase vs placebo) with respect to peak excretion, peak minus (-) the baseline and total BH output (AUC). Whether a comparison of the mean or of the median is carried out, ANOVA results showed significant treatment effects for all 3 parameters or evaluations: peak (p-value ≤ 0.001), peak minus baseline (p-value $= 0.014$), and AUC (p-value ≤ 0.001).

- In this study, there were no statistically significant differences between enzyme and placebo in g.i. symptoms (diarrhea, gas, bloating or cramps) experienced during and up to 8h after the BHT. The majority of patients in each treatment group (82 for placebo, 91% for enzyme) had a total symptom score (sum of maximum severity scores for each symptom) of six or less.

- As computed in Table 10, therapeutic gains were shown in the percentage of patients that reported no symptoms for three (diarrhea, gas and bloating) of the four symptoms assessed. But these numerical advantages were not statistically significant when the data were analyzed by the Wilcoxon signed-rank test. The results for cramps were identical for both experimental groups.

TABLE 10
Study S-1 (OMC-SUC-1)
Breath Hydrogen Phase
Percentage of Patients With no Gastrointestinal Symptoms
(Abstracted from Table 7.1)

Treatment	Symptom			
	Diarrhea	Gas	Bloating	Cramps
Placebo	73%	82%	82%	73%
Sucrase	55%	55%	64%	73%
Therapeutic Gain	-18%	-27%	-18%	0%
p-value[a]	N.S.	N.S.	N.S.	---

This Table was abstracted from sponsor's Table 7.1, with major modifications.
a) Wilcoxon signed-rank test

b) Dose Response Phase

- The sponsor presented data on stool counts and stool consistency measures in their Table 8.0. From this, the information summarized in Table 11 has been abstracted. There were some numerical but neither clinically nor statistically significant differences between the treatment groups.

TABLE 11
Study S-1 (OMC-SUC-1)

Dose-Response Phase: Mean Number of Stools

Treatment (Dilution)	Number of Stools					
	Total	Average/Day	Watery	Soft	Formed	Hard
1:100	24.5	1.77	6.8	6.9	7.3	2.1
1:1000	20.0	1.44	5.6	6.5	5.5	2.2
1:10,000	24.4	1.76	7.3	8.5	7.2	1.4
1:100,000	22.7	1.69	7.6	6.8	6.6	1.6

This Table was abstracted from sponsor's Table 8.0, with major modifications. The ± S.E.M. has been omitted for simplification of presentation purposes.

- Average scores for g.i. symptoms are presented in Table 12. Some numerical differences between groups can be appreciated (upper panel of Table 12). However, as shown in the lower panel of this Table, significant pairwise treatment differences were observed between the 1:100 and 1:100,000 dilutions [A vs D] only with respect to the average daily abdominal cramps (p-value=0.031). Results did not indicate significant treatment differences for any of the outcome variables when comparing the two more concentrated solutions (1:100 and 1:1000 dilutions) with the two less concentrated solutions (1:10,000 and 1:100,000 dilutions). No other p-values were significant for any of the remaining efficacy variables.

[NOTE: Total scores for g.i. symptoms, presented in sponsor's Table 9.0 yielded results similar to those of the average scores.]

TABLE 12
Study S-1 (OMC-SUC-1)
Dose-Response Phase: Average Scores of Gastrointestinal Symptoms

Symptom[a]	Treatment Group/Dilution			
	1:100 [A] [n=13]	1:1000 [B] [n=13]	1:10,000 [C] [n=13]	1:100,000 [D] [n=13]
	Average Scores of Gastrointestinal Symptoms			
Gas [n →]	13	11	13	11
0	1 (8%)[b]	3 (27%)	2 (15%)	3 (27%)
>0-0.3	2 (15%)	3 (27%)	3 (23%)	1 (9%)
>0.3-0.7	6 (46%)	2 (18%)	1 (8%)	4 (36%)
>0.7-1.1	1 (8%)	1 (9%)	4 (31%)	2 (18%)
>1.1	3 (23%)	2 (18%)	3 (23%)	1 (9%)
Bloating [n →]	13	11	13	11
0	6 (46%)	6 (55%)	4 (31%)	5 (45%)
>0-0.3	4 (31%)	2 (18%)	4 (31%)	3 (27%)
>0.3-0.7	1 (8%)	2 (18%)	3 (23%)	2 (18%)
>0.7	2 (15%)	1 (9%)	2 (15%)	1 (9%)
Nausea [n →]	13	11	13	11
0	12 (92%)	7 (64%)	11 (85%)	9 (82%)
>0-0.3	0	4 (36%)	1 (8%)	1 (9%)
>0.3-0.7	1 (8%)	0	1 (8%)	1 (9%)
>0.7	0	0	0	0
Vomiting [n →]	13	11	13	11
0	13 (100%)	11 (100%)	13 (100%)	9 (82%)
>0	0	0	0	2 (18%)
Cramps [n →]	13	11	13	11
0	5 (38%)	7 (64%)	8 (62%)	9 (82%)
>0-0.3	4 (32%)	1 (9%)	2 (15%)	1 (9%)
>0.3-0.7	3 (23%)	1 (9%)	2 (15%)	1 (9%)
>0.7	1 (8%)	2 (18%)	1 (8%)	0

	Statistics: Treatment Comparisons = p-value[c]						
	A vs B	A vs C	A vs D	B vs c	B vs D	C vs D	A and B vs C and D
Gas[d]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Bloating[d]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Nausea[d]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Vomiting[d]	----	----	N.S.	----	N.S.	N.S.	N.S.
Cramps[d]	N.S.	N.S.	**0.031**	N.S.	N.S.	N.S.	N.S.

This Table is based on sponsor's Tables 9.1 and 10, put together, with major modifications.
a) Severity scores averaged over a 14-day period. Original scale: 0=None, 1=Mild, 2=Moderate, 3=Severe.
b) Percentages are based on the number of patients with nonmissing data for that symptom.
c) p-value obtained from a nonparametric Wilcoxon signed-rank test on pairwise treatment comparisons
d) Based on average severity scores over a 14-day period.

c) Responder Analysis (Table 13)

As shown in this Table, during the dose-response treatment period, a higher percentage of patients were asymptomatic while receiving the 1:1000 enzyme dilution (45%) than while receiving the other dilutions. However, no significant pairwise treatment differences (nonparametric McNemar's test) were found in this analysis.

TABLE 13
Study S-1 (OMC-SUC-1)

Dose-Response Phase: Responder Analysis

Measurement	Treatment Group/Dilution			
	1:100 [A] [n=13]	1:1000 [B] [n=13]	1:10,000 [C] [n=13]	1:100,000 [D] [n=13]
Asymptomatic[a]	13	11	13	11
YES	3 (23%)b	5 (45%)	5 (38%)	4 (36%)
NO	10 (77%)	6 (55%)	8 (62%)	7 (64%)

Statistics

Treatment Comparisons:	p-value[c]
A vs B	N.S.
A vs C	N.S.
A vs D	N.S.
B vs C	N.S.
B vs D	N.S.
C vs D	N.S.

This Table corresponds to sponsor's Table 11, with major modifications.
a) A patient was asymptomatic if on at least 70% of the days in a period with nonmissing data, he/she had no watery stools and ratings of none or mild for all gastrointestinal symptoms.
NOTE: Two patients missed two treatment periods. Six patients had missing data on one or more days.
b) Percentages are based on the number of patients with nonmissing data for that period.
c) p-value obtained from a nonparametric McNemar's test on pairwise treatment comparisons.

D. Safety

Treatment with yeast sucrase was well-tolerated. In this study, there were neither deaths, nor discontinuations due to AEs. No patient experienced serious or severe AEs.

12. Sponsor's Conclusions

"Following the ingestion of sucrose, yeast sucrase inhibits the expected rise in breath hydrogen excretion, when compared to placebo. Mean breath hydrogen output was markedly lower for yeast sucrase than for placebo at every time point over the three-hour period, as well as for peak, peak minus baseline, and total breath hydrogen output. Furthermore, highly significant treatment

effects were present between placebo and yeast sucrase (flavoring sucrase) for all three measures of breath hydrogen excretion namely, peak, peak minus baseline, and total breath hydrogen output.

"The results of this trial suggest that yeast sucrase appears to be an effective treatment for the reduction of gastrointestinal symptoms in patients with CSID. While it is evident that the a:1000 dilution of yeast sucrase was most often associated with fewer total stools and lower severity scores, results pertaining to the 1:100, 1:10,000 and 1:100,000 dilutions were favorable, overall. There were no consistent dose related changes that were significant. Treatment with yeast sucrase was well-tolerated, with no patients discontinuing due to adverse effects and no patients experiencing any serious adverse effects. Thus, yeast sucrase appears to be safe and efficacious in treating patients with congenital sucrase-isomaltase deficiency."

13. Reviewer's Additional Comments

Data from Study S-1 (OMC-SUC-1) were submitted by the sponsor as one of the two adequate and well-controlled main trials in support of the approval of SUCRAID™ (sacrosidase) for the treatment of congenital sucrose isomaltase deficiency. Study S-1 was a randomized, double-blind, crossover trial which consisted of two phases: the breath hydrogen test (BHT) and the dose-response test. The BHT consisted of two single-dose treatments: placebo and liquid yeast sucrase (YS) which were given in random order. The dose-response phase consisted of four consecutive 14-day treatments; four dilutions of the enzyme (1:100; 1:1000; 1:10,000 and 1:100,000) that were administered to each patient in a random sequence.

The study population was adequate for the proposed study and indication being sought (see Reviewer's Additional Comments to Study S-2). In all children randomized into the trial the diagnosis of CSID was confirmed by disaccharidase level criteria (DEA) (sucrase activity of <10% of controls with normal lactase levels and normal or decreased maltase activity) measured in duodenal mucosal samples collected upon upper g.i. endoscopy, breath hydrogen test (BHT) or DEA + BHT. Of 16 patients screened, 13 comprised the efficacy population and 14 the safety population.

The BH phase consisted of one week (two single doses given one week apart) while the dose-response phase consisted of eight weeks (14 days on each of the four sucrase dose levels). There were no washout periods between the treatments (four dilutions of the enzyme).

In Study S-1, the criteria for evaluation of efficacy were adequate and consisted of both primary and secondary efficacy parameters. The primary efficacy variables included total stools and the total symptoms score, collected during the dose-response phase. The secondary efficacy variables included peak, peak minus baseline, and total BH output (area under the BH curve), as well as individual and total symptoms scores (from the BH phase); and total watery, soft, formed, and hard stools, average daily stools, average

and total individual symptom scores, average total symptoms scores, and asymptomatic, defined post-hoc (from the dose-response phase).

The results of Study S-1 were inconsistent and not very impressive. With regard to the primary efficacy parameters, there was no dose-response relationship. Although the 1:1000 dilution was the treatment most associated with fewer total stools there was no statistically significant difference for any pairwise comparison or the comparison of the two lower vs the two highest dilution strengths for total stools or the average stools per day. Similarly, except for significant pairwise comparison between the 1:100 and 1:100,000 dilutions ($p=0.020$), there were no significant treatment differences between other pairwise comparisons or comparisons between the two lower vs the two higher concentrations of enzyme for total symptoms.

Similarly, analysis of the results of secondary parameters did not support efficacy. During and up to 8h of the BH test phase, there were no statistically significant differences between enzyme and placebo in g.i. symptoms (diarrhea, gas, bloating or cramps). With regard to average g.i. scores during the dose-response phase, some numerical differences between the groups were appreciated but except for the comparison between the 1:100 vs the 1:100,000 dilutions ($p=0.031$ with respect to the daily abdominal cramps) the results did not indicate significant differences for any of the outcome variables when comparing the two more concentrated vs the two less concentrated solutions.

The only important contribution from Study S-1 appeared to be an effect of BH excretion. In this Study, YS markedly significantly inhibited the expected rise in BH excretion, when compared to placebo. Mean BH output was considerably lower for yeast sucrase than for placebo at every time point over the 3-h period, as well as for peak, peak minus baseline, and total BH output. Statistically significant treatment effects were present between placebo and sucrase (favoring YS) for peak, peak minus baseline, and total breath hydrogen output.

In Study S-1, treatment with yeast sucrase was well-tolerated.

In summary, Study S-1 failed to meet the objectives of the trial set up in the protocol. Objective 1 ("to further characterize the activity, pH, and temperature stability, purity, and proper storage of the liquid sucrase preparation") was never addressed in the clinical protocol. Objective 2 was partly met. This is because efficacy of the liquid sucrase preparation in abolishing or ameliorating diarrhea, flatulence and abdominal pain was not shown, although a significant decrease in breath hydrogen excretion in patients with CSID given an oral sucrose challenge was demonstrated. The study also failed objective 3 since a dose range of the yeast-derived liquid sucrase preparation, which would allow the consumption of a normal sucrose-containing diet was not really established. Although of some utility, results of Study S-1 alone cannot be used in support of the approval of liquid YS treatment for CSID patients.

VIII. STUDY S-2 (OMC-SUC-2)[33]

Sucrase Enzyme Therapy for Sucrase-Isomaltase Deficiency

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1. Objectives

In the protocol, the following was included under A. SPECIFIC AIMS:

> The objective of this study is to test the efficacy of yeast-derived liquid sucrase in treating patients with congenital

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sucrase-isomaltase deficiency (CSID). The specific hypotheses to be tested are:

1) Yeast sucrase (YS) will prevent or blunt the expected rise in breath hydrogen (H_2) excretion when a patient with CSID ingests a large sucrose load, and

2) YS will prevent the expected gastrointestinal symptoms of cramps, excessive gas, and diarrhea when a patient with CSID ingests a diet containing normal amounts of sucrose.

NOTE: Study S-2 resembles S-1 in most respects, re: design and execution. Therefore, only certain aspects of the design and execution of Study S-2 will be repeated or highlighted here.

2. Study Population (Table 14)

In Study S-2, the study population was, in essence, as in Study S-1, but now specific reasons for exclusion were listed (Table 14). Included in the trial were patients with confirmed CSID, who were of any age, gender or ethnicity and who provided IC [or, if patient was younger than 18y old, the IC was provided by the parent/guardian].

TABLE 14
Study S-2 (OMC-SUC-2)

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• Patients were recruited nationally, by participating gastroenterologists, through the Principal Investigator's colleagues in the North American Society for Pediatric Gastroenterology and the American Gastroenterological Association. • Patients of any age (sponsor's Appendix 18.1) diagnosed with CSID as determined by the following criteria: 1) appropriate clinical history 2) small intestinal biopsy with measurement of disaccharidase levels showing sucrase activity of <10% of controls with normal lactase levels and normal or decreased maltase activity, 3) normal villous architecture of the small intestine, 4) normal lactose breath hydrogen test. • No lactose intolerance. • No chronic illnesses or pregnancy. • Informed consent of self or of a parent/guardian, if the patient was younger than 18y old.	• Other chronic medical illnesses. • Other chronic medical therapy. • Pregnancy • Lactose intolerance • Inability to understand the risks and parameters of the trial (or such inability by the parent/guardian).